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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,952	LEPPLA ET AL.	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/22/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *2-3, 6, 10, 15-16, and 23-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,7-9,11-14,17-22 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The response filed on October 22, 2004 to the restriction requirement of August 25, 2004 has been received. Claims 1-29 are currently pending in this application. Claims 2-3, 6, 10, 15-16, and 23-24 have been withdrawn by applicant. Applicant's have elected Group II, claims 1, 4-5, 7-9, 11-14, and 17-22, as specifically drawn to a therapeutic method of targeting a native lethal factor to a cancer cell over-expressing a plasminogen activator or a plasminogen activator receptor. Applicant's have further elected the following sequence from claim 7: PGSGRSA.

Applicant's election with traverse of Group II, claims 1, 4-5, 7-9, 11-14, and 17-22, drawn to a therapeutic method of targeting a native lethal factor to a cancer cell overexpressing a plasminogen activator or a plasminogen activator receptor is acknowledged. The traversal is on the ground(s) that the nine groups set forth by the Examiner are linked by a single general inventive concept in that each stem from the general inventive concept of targeting a compound to a cell by administering both a ***mutant*** protective antigen and a lethal factor polypeptide comprising a protective antigen binding site to the cell. The applicants further argue that the mutant protective antigen comprises a mutation wherein the native furin-recognized cleavage site has been replaced with a cleavage site for another protease, i.e., a matrix metalloproteinase or a plasminogen activator and that the protective antigen cleave site is cleaved by the non-furin protease and binds to lethal factor, thereby translocating the lethal factor into the cell. Thus, the applicants believe that all the claims require a mutant protective antigen wherein the native furin-recognized cleavage site has been replaced with a cleavage site for another protease and as such, are linked by a common technical concept, i.e., a mutant anthrax protective antigen comprising a non-furin cleavage site. These arguments have been considered and not found persuasive.

In the instant case, there appears to be not one mutant protective antigen, which is required by all of the claims, but two wherein the native-furin cleavage site has been replaced with either a cleavage site for a matrix metalloprotease or for a plasminogen activator. Thus, the mutant protective antigen do not possess a common technical concept because a cell over-expressing a plasminogen activator or plasminogen activator receptor may not recognize a mutant protective antigen comprising a matrix metalloproteinase and *vice versa.*

For these reasons, the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-29 are currently pending.

Claims 2-3, 6, 10, 15-16, and 23-24 have been withdrawn by the Applicant.

Claims 1, 4-5, 7-9, 11-14, 17-22, and 25-29 are currently under examination.

Species Election

The election of species is no longer required.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 is drawn to a method of targeting a compound to a cell over-expressing a matrix metalloproteinase and administering a mutant protective antigen protein comprising a matrix metalloproteinase which are non elected inventions.

Claim 7 is objected to because of the following informalities: Claim 7 is drawn to a method of claim 1, wherein the plasminogen activator recognized cleavage site is selected from the group consisting of PCPGRVVGG, PGSGKSA, and PQRGRSA which are non elected inventions.

Claim 7 is further objected for improper disclosure of an amino acid sequence without a respective sequence identifier, i.e. a SEQ ID NOs:.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5, 7-9, 11-14, 17-22, and 25-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of targeting a compound to a cancer cell over-expressing a plasminogen activator or plasminogen activator receptor comprising the steps of administering to the cell a mutant protective antigen comprising the plasminogen activator recognized cleavage site consisting of the amino acids PGSGRSA (SEQ ID NO: 5), wherein the plasminogen activator is u-PA, does not reasonably provide enablement for a method of targeting a compound to cells over-expressing a plasminogen activator or plasminogen activator receptor comprising the steps of administering to the cell a mutant protective antigen comprising a plasminogen activator recognized cleavage site consisting of PGSGRSA (SEQW ID NO: 5), wherein the plasminogen activator is t-PA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working

examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, the claims are broadly drawn to a method of targeting a compound to a cell over-expressing a plasminogen activator or a plasminogen activator receptor comprising administering to a cell a mutant protective antigen protein comprising a plasminogen activator recognized cleavage site set forth as PGSGRSA (SEQ ID NO: 5), wherein the plasminogen activator is either t-PA or u-PA.

Thus, this would imply that the plasminogen activator recognized cleavage site set forth in SEQ ID NO: 5 would be recognized by either plasminogen activators, i.e. t-PA or u-PA.

However, one cannot extrapolate the teachings of the specification with the scope of the claims because the claims are drawn to a system for targeting a compound to a cell over-expressing either a plasminogen activator or a plasminogen activator receptor comprising administering a mutant protective antigen protein comprising a plasminogen activator-recognized cleavage site comprising the amino acids PGSGRSA (SEQ ID NO: 5). The specification provides insufficient guidance and or objective evidence that the plasminogen activator, tPA, would recognize the cleavage site. The specification teaches (page 48, lines 5-34) that mutated PA protein were constructed wherein the furin recognized cleavage site, $RKKR_{167}$ (SEQ ID NO: 1), is replaced by a uPA or tPA substrate sequence. For example, in the mutant PA-U2, $RKKR_{167}$ (SEQ ID NO: 1) was replaced by a peptide, PGSGRSA (SEQ ID NO: 5) containing the consensus sequence SGRSA (SEQ ID NO: 22) from P3 to P2', which was recently identified as the minimized best substrate for uPA. The specification in the same section further discloses that because the peptide SGRSA (SEQ ID NO: 22) is cleaved 1363 fold times more efficiently than a control peptide containing the physiological cleavage site present in plasminogen by uPA, and exhibits a uPA/tPA selectivity of 20, PA-U2 is expected to be a favorite substrate of uPA. The specification further teaches (page 52, lines 12-15) that PA-U4 was toxic to the two tPA expressing cells (*e.g. good substrate*), while PA-U2 and PA-U3 showed a very low toxicity to them, clearly showing that uPA and tPA susceptibility differentiate among these mutated PA proteins. Therefore, in view of the disclosure, the breadth of the claims and the absence of working examples, it would require

undue experimentation for one skilled in the art to practice the invention as claimed in the scope of the present claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-5, 8, 11-14, 18-22 and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leppla et al. (IDS, 1997) in view of Bayley *et al.* (IDS, 1998).

In the instant case, the claims are drawn to a method of targeting a compound to a cell over-expressing a plasminogen activator or a plasminogen activator receptor, the method comprising the steps of: (i) administering to the cell a mutant protective antigen protein comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site, wherein the mutant protective antigen is cleaved by a plasminogen activator; and (ii) administering to the cell a compound comprising a lethal factor polypeptide comprising a protective antigen binding site; wherein the lethal factor polypeptide binds to cleaved protective antigen and is translocated into the cell thereby delivering the compound to the cell (Claim 1). The cell is further limited to over-expressing a plasminogen activator receptor and is either a human cell or cancer cell (Claims 8 and 9). The lethal factor polypeptide is further limited to being native lethal factor or linked to a heterogeneous compound which can be recombinantly linked to a lethal factor or comprises amino acids 1-254 of native lethal factor linked either recombinantly or covalently to a heterogeneous compound wherein the heterogeneous compound is the ADP-ribosylation domain of Pseudomonas exotoxin A (Claims 11, 13, 25-29). The compound is further limited to shiga toxin, A chain of diphtheria toxin or Pseudomonas exotoxin A, a diagnostic or a therapeutic agent (Claims 12, 14, and 19). The mutant protective antigen protein is further limited to a fusion protein comprising a heterologous receptor-binding domain,

wherein the heterologous receptor-binding domain is either a single chain antibody or a growth factor (Claims 21-22).

Leppla *et al.* teach (column 115, lines 410-63) a method for targeting compounds having a desired biological activity not present on native anthrax lethal factor (LF) to a specific cell population, comprising: a) administering to the cell population a first compound comprising a first protein consisting essentially of: i) the translocation domain and the anthrax lethal factor (LF) binding domain of the native anthrax protective antigen (PA) protein, and ii) a ligand domain that specifically binds the first protein to a target on the surface of the cell population to bind the first compound to said surface; and b) administering to the resultant cell population a second compound comprising a fusion protein or conjugate consisting essentially of: i) the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein, chemically attached to ii) a biological activity-inducing polypeptide to bind the second compound to the first compound on the surface of the cell population, internalize the second compound into the cell population, and effect the activity of the polypeptide therein. The patent further teaches (Column 116, lines 42-44, 53-56, and 63-64) that the ligand domain of the first compound can be either the ligand domain of the native anthrax protective antigen (PA) protein or growth factor, or an antibody, wherein the antibody is a single chain antibody. Furthermore, Leppla *et al.* disclose (column 115, lines 64-67 and column 116, lines 40-41) that the anthrax protective antigen (PA) binding domain of the second compound comprising at least the first 254 amino acid residues but less than all of the amino acid residues of the native anthrax lethal factor. Moreover, the patent teaches (column 116, lines 51-52) that the second compound may comprise the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein chemically attached to a polypeptide through a peptide bond. In addition, Leppla *et al.* teach (column 116, lines 49-52 and 57-62) that the polypeptide of the second compound is an enzyme or a toxin, wherein the toxin can be Pseudomonas exotoxin A (PE), A chain of Diptheria toxin, or shiga toxin. With regards to Pseudomonas exotoxin A, the patent teaches (column 17, lines 15+) that anthrax lethal toxin is linked to the ADP-Ribosylation Domain of Pseudomonas exotoxin. Leppla *et al.* also disclose (Abstract, last sentence) proteins including an anthrax protective antigen which has been mutated to replace the

trypsin cleavage site with residues recognized specifically by the HIV-1 protease. Specifically, the patent teaches (column, 11, lines 10-13) PA proteins which have been mutated to replace R164 to 167 with an amino acid sequence recognized by the HIV-1 protease. In addition, the patent teaches (column 1, lines 24-26) that in a therapeutic or diagnostic setting, the used of an sFv may offer attractive advantages over the use of monoclonal antibodies. Lastly, Leppla *et al.* teach (column 15, lines 27-37) that this methodology can be used to specifically killing a tumor cell in a subject.

Leppla *et al.* does not disclose a mutated protective antigen comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site.

Bayley *et al.* teach (column 12, lines 13+) the construction of Ab-αHL conjugates and mutated two chain αHL conjugates, wherein a protease can be employed as an activator of inactive compounds, e.g. plasminogen activator, specifically urokinase-type plasminogen activator (uPA). Specifically, the patent teaches (column 12, lines 13+) that because cancer cells have been shown to secrete plasminogen activator, the protease cleavage site for plasminogen activator can be incorporated into the conjugate for specific activation of this cell type.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate a plasminogen activator-protease cleavage site in place of the native protective antigen furin-recognized cleavage site as a way of targeting a compound to a cancer cell over-expressing a plasminogen activator or plasminogen activator receptor. One would have been motivated to make this substitution because Bayley *et al.* teach that it is well known in the art that a plasminogen activator, such as uPA, can be employed as an activator of an inactive agent such as the protective antigen protein of Leppla *et al.*. One of ordinary skill in the art would have reasonable expectation of success that by combining the plasminogen activator-recognized cleavage site of Bayley *et al.* with the method of specifically targeting a bioactive compound taught by Leppla *et al.*, one would achieve a method of specifically targeting a compound to a cancer cell because as evidenced by Bayley et al., cancer cells have been shown to secrete plasminogen activator.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

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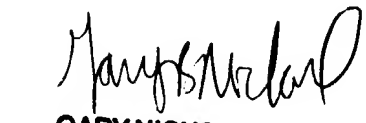

GARY NICKOL
PRIMARY EXAMINER